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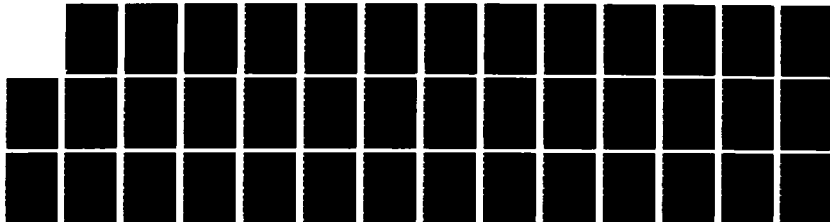
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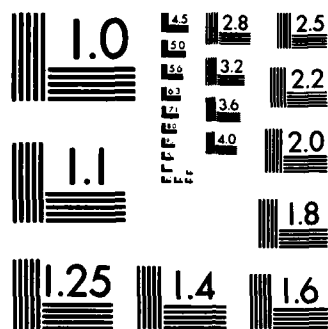
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) ATTACHED.		

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## I. INTRODUCTION

### A. Literature Review

Tocainide is a primary amine analog of lidocaine which, in contrast to lidocaine, can be administered both orally and intravenously. Orally administered tocainide is effective in suppressing both chronic stable ventricular arrhythmias and life threatening ventricular arrhythmias refractory to conventional antiarrhythmic drug therapy.<sup>1,7,13</sup> Intravenously administered tocainide has been used successfully in the treatment of ventricular arrhythmias after acute myocardial infarction.<sup>2</sup>

Tocainide is a Class 1B antiarrhythmic agent that shortens the action potential duration and the effect refractory periods of the atria, atrioventricular node, and ventricles.<sup>11</sup> It has little effect on sinus nodal automaticity or intracardiac conduction. Although PR and QRS intervals are usually unchanged, tocainide may reduce the QT interval. Cardiac hemodynamic effects are minor, even in patients with moderate left ventricular dysfunction or those also receiving a beta-adrenergic agonist.<sup>3</sup>

The chemical structure of tocainide includes an asymmetric center and the drug is used clinically in the racemic form. Although the antiarrhythmic properties of the tocainide enantiomers have not been studied in man, the R-(-) enantiomer is three times more potent than the S-(+)

PHARMACODYNAMIC EFFECTS OF R-(-) AND S-(+) TOCAINIDE  
IN PATIENTS WITH CHRONIC VENTRICULAR ARRHYTHMIAS

A Research Report Presented  
to the School of Pharmacy  
& Allied Health Professions  
of Creighton University

In Partial Fulfillment of the  
Requirements for the Degree  
of Doctor of Pharmacy

by

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April, 1986

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## DEDICATION

This investigational project and academic accomplishment is dedicated to Patsy, Jason, and Denise, whose love, understanding, and encouragement supported me.

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I would like to thank my advisor, Daniel E. Hilleman for his guidance given throughout this learning experience.

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## I. INTRODUCTION

### A. Literature Review

Tocainide is a primary amine analog of lidocaine which, in contrast to lidocaine, can be administered both orally and intravenously. Orally administered tocainide is effective in suppressing both chronic stable ventricular arrhythmias and life threatening ventricular arrhythmias refractory to conventional antiarrhythmic drug therapy.<sup>1,7,13</sup> Intravenously administered tocainide has been used successfully in the treatment of ventricular arrhythmias after acute myocardial infarction.<sup>2</sup>

Tocainide is a Class 1B antiarrhythmic agent that shortens the action potential duration and the effect refractory periods of the atria, atrioventricular node, and ventricles.<sup>11</sup> It has little effect on sinus nodal automaticity or intracardiac conduction. Although PR and QRS intervals are usually unchanged, tocainide may reduce the QT interval. Cardiac hemodynamic effects are minor, even in patients with moderate left ventricular dysfunction or those also receiving a beta-adrenergic agonist.<sup>3</sup>

The chemical structure of tocainide includes an asymmetric center and the drug is used clinically in the racemic form. Although the antiarrhythmic properties of the tocainide enantiomers have not been studied in man, the R-(-) enantiomer is three times more potent than the S-(+)

isomer as an antiarrhythmic agent in a mouse model and smaller differences in antiarrhythmic activity between the enantiomers have been demonstrated in coronary-ligated dogs.<sup>4,6</sup> Studies done by Sedman et al, looking at R-(-) and S-(+) ratios over a three year period of tocainide administration found the R:S ratio to range from 0.77 to 0.25. They also found that intrasubject variability of enantiomer ratio was as large as the variability between subjects and that clinical parameters such as tocainide dosage, other medications, or degree of congestive heart failure, renal failure, or hepatic dysfunction, did not explain enantiomer variability.<sup>4</sup>

The reported range for total tocainide therapeutic concentration is 4-12 ug/ml. Assuming that only one enantiomer is active, correlation of antiarrhythmic effect may be primarily the result of the concentration of the R-(-) enantiomer.<sup>4</sup> Monitoring this enantiomer's concentration may be more beneficial than monitoring total tocainide concentration.

#### B. Statement of the Problem

Tocainide is administered as a 1:1 mixture of an R-(-) and S-(+) enantiomer. Studies in animals have shown the R-(-) enantiomer to be three times more potent than the S-(+) enantiomer. Only one study has looked at how R-(-) and S-(+) concentrations change over time in man. No studies in humans have been done to see how the enantiomer

concentrations correlate with antiarrhythmic response.

### C. Purpose of the Project

This project will investigate the data collected to see if a correlation exists between the following variables:

1. Concentration of tocainide versus arrhythmia response
2. Concentration of R-(-) enantiomer versus arrhythmia response
3. Concentration of S-(+) enantiomer versus arrhythmia response
4. R:S ratio versus arrhythmia response

## II. HYPOTHESIS

- $H_0$ : There is no correlation between concentration of tocinide or its enantiomer and arrhythmia response.
- $H_a$ : There is a correlation between concentration of tocinide or its enantiomers and arrhythmia response.

### III. METHODOLOGY AND PROCEDURES

#### PATIENT IDENTIFICATION

##### Inclusion Criteria

1. Males and females, 18-70 years of age. Females were postmenopausal or permanently sterilized.
2. Patients exhibited on EKG six or more VPBs/minute and/or VT. VT was defined as three or more consecutive VPBs with a rate of >100 beats/minute.

##### Exclusion Criteria

1. Subject was in a situation or had a condition which, in the investigator's opinion, could have interfered with optimal participation in the study or produced a significant risk to the subject.
2. Patients who manifested evidence by history or physical examination of the following specific conditions:
  - a. Grade II or III AV block.
  - b. Sick sinus syndrome; ventricular pre-excitation; atrial flutter or fibrillation, atrial tachycardia.
  - c. Patients with pacemakers.
3. Any patient who experienced arrhythmias resulting from cardiothoracic surgery.
4. Patients who had history of sensitivity to amide-class local anesthetics.
5. Patients who were on other antiarrhythmic agents (except digoxin, calcium channel blockers and beta-blocking drugs, if the indication for their use was not ventricular arrhythmias) and/or experimental or



investigational drugs.

6. Patients who exhibited evidence of alcohol or drug dependence.
7. Patients who had drug toxicity or electrolyte imbalance.
8. Any patient who had clinically significant laboratory values at entry into the study (excluding abnormal CPK, LDH, SGOT, SGPT). Table II

#### CONDITIONS THAT REMOVED PATIENTS FROM THE STUDY

1. Any severe adverse reaction.
2. Life-threatening arrhythmias that required institution of immediate treatment.
3. Development of any significant concurrent illness that required other therapy which may have interfered with tocainide treatment.
4. Patients who refused or failed to take prescribed medication.
5. Any other reason at the discretion of the principal investigator.

#### SAMPLE POPULATION

There were 15 patients, 13 males and 2 females, with chronic ventricular arrhythmias, entered into the study (Table I). Cardiac diagnoses included coronary artery disease in 10 patients, cardiomyopathy in 4 patients, valvular heart disease in 1 patient, congestive heart failure in 6 patients, and prior myocardial infarction in 6 patients. Mean age of the group was  $60 \pm 8$ .

### INVESTIGATIONAL PROCEDURES

Patients were hospitalized in the coronary care unit and baseline documentation of the arrhythmic was obtained from on-line computerized arrhythmia monitoring.

All patients received the same dose of intravenous tocainide in a 3-step method: 1) 250mg bolus over 2 minutes; 2) 500mg loading infusion over 15 minutes; and 3) a maintenance infusion of 500mg every six hours (1.39mg/min) for 48 hours. Blood samples were taken for plasma concentration determinations of tocainide and each of its enantiomers before treatment (baseline) and after 2 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, and 48 hours (Table III). Ten ml of blood was obtained in a heparinized tube for each scheduled sample time. Blood pressure, pulse rates, and respirations were monitored prior to administration of the drug and just before the times blood samples were drawn. A 12-lead EKG was performed on admission to the study and at the study conclusion.

For data analysis, responders were defined as those patients having a 75% or greater reduction in VPBs based on the frequency at admission to the study. Serum concentrations will be compared with the percent of responders and percent reduction in VPBs (Table IV).

## IV. RESULTS

A summary of the results of this study are contained in Table V. The average tocainide concentration for the first hour (Graph 1) was  $3.5 \pm 1.5$  mcg/ml and increased over the study period to an average concentration of  $7.8 \pm 2.7$  mcg/ml at the 40th hour. Average concentration decreased over the last 8 hours of the study to  $6.0 \pm 1.5$  mcg/ml. The average R-(-) enantiomer concentration for the first hour was  $1.7 \pm 1.0$  mcg/ml compared to the S-(+) enantiomer concentration of  $1.8 \pm 1.1$  mcg/ml (Graph 1). The R-(-) to S-(+) ratio at the first hour was 0.94 (Graph 2). Concentrations of the R-(-) and S-(+) enantiomers increased to  $2.8 \pm 1.0$  mcg/ml and  $5.0 \pm 0.9$  mcg/ml, respectively. The concentrations of the R & S enantiomers also fell over the last eight hours of the study period to  $2.0 \pm 0.7$  mcg/ml and  $4.0 \pm 0.3$  mcg/ml. R-(-) to S-(+) ratio at the end of the study was 0.50.

Responders were defined as a 75% or greater reduction in ventricular premature beats (VPB's). Thirty-eight percent of patients were responders in the first hour (Graph 3) but decreased to 31% during the second hour. During the 4th hour, 50% of the patients were responders and during the 40th hour, 62% of the patients responded to tocainide. A decrease in the number of patients responding occurred over the last eight hours of therapy but was still greater than 50%. The mean percent of responders over the 48 hour study period was  $55 \pm 10$ %.

The average reduction in VPB's for all patients during

the first hour was 21% and increased to 35% during the second hour. Average reduction in VPB's fell during the fourth hour of therapy to 22%. The highest average reduction in total VPB's for all patients occurred 16 hours into therapy with 63% reduction in VPB's. Mean reduction in VPB's during the entire study was  $44 \pm 14\%$ .

An excellent relationship existed between total tocainide concentration and the percent of patients responding (Graph 4). For this data a correlation coefficient ( $r$ ) of 0.84 ( $p < 0.01$ ) was calculated. A good relationship also existed between the total tocainide concentration and percent suppression of VPBs (Graph 5). Calculated correlation coefficient for this data was 0.74 ( $p < 0.01$ ).

Correlation coefficients ( $r$ ) for the R-(-) and S-(+) enantiomers and the percent of patients responding were 0.86 ( $p < 0.001$ ) and 0.81 ( $p < 0.01$ ), respectively (Graphs 6).

The correlation coefficient ( $r$ ), calculated to be -0.74 ( $p < 0.01$ ), was moderately suggestive of an inverse relationship existing between the R-(-):S-(+) ratio and the percent reduction in VPBs, i.e. as the ratio decreased the percent reduction of VPBs increased (Graph 8). At a R-(-):S-(+) ratio of 0.94 only 21% of VPBs were suppressed while at a R-(-):S-(+) ratio of 0.67 there was a 63% suppression of VPBs.

## V. DISCUSSION

Quantitative analysis of VPB frequency on a large number of ambulatory electrocardiogram tapes has demonstrated that VPB frequency in any given patient can be highly variable, with wide spontaneous fluctuations in any given individual.<sup>5,7-9</sup> This spontaneous variability, as demonstrated in this study by the differences in VPB frequency documented for each patient over the 48 hour study period, may obscure accurate determination of a plasma-antiarrhythmic effect relationship for any given individual patient. Construction of a plasma concentration response curve requires reconsideration of the meaning of a therapeutic plasma concentration. The antiarrhythmic effect of tocainide is not an all-or-none phenomenon, but is continuous over a range of plasma concentrations.<sup>5</sup>

Winkle, et al, stated that, for a group of responders, 70% or greater suppression of VPB's was achieved when plasma concentration of tocainide was above 6.0mcg/ml, with 90% suppression of VPB's achieved at plasma concentrations greater than 10mcg/ml.<sup>12</sup> This study showed that, for our group of responders, the concentration for 75% or greater reduction in VPB's could be achieved at a lower concentration in some patients. Almost 40% of our patients responded to tocainide with greater than 75% suppression of VPB's at a concentration of 3.5mcg/ml. This may suggest that some patients or arrhythmias may be more sensitive to

the effect of tocainide and may require serum drug monitoring only in those patients or arrhythmias refractory to tocainide. This data also supports the theory that one particular dose of tocainide should not be given to all patients but the lowest dose possible initiated and titrated upwards.

If we assume that for an antiarrhythmic to be efficacious it must suppress VPB's by greater than 75% in at least 50% of the patients, tocainide was effective in this study at concentrations greater than 5.3mcg/ml. This seems to correlate with the data reported by Winkle, et al.<sup>12</sup> Other studies, such as those done by Morganroth, et al, defined antiarrhythmic efficacy to be 80% or greater reduction in single VPB's. Their studies reported the efficacy of tocainide occurred in 55% of 36 patients over a 24 hour study period.<sup>1,11</sup> This data supports our study in which we also had a mean success rate of  $55 \pm 10\%$  over the 48 hour study period. Morganroth also observed complete abolition of VPB's in 38% of their patients. In our study, 33% of the patients had complete abolition of VPB's, but this response did not occur until 32 hours into the study where the mean concentration was  $7.3 \pm 2.8$ mcg/ml. Only 14% of our patients had complete abolition of VPB's the first hour.

The purpose of this paper was not to study the individual kinetics of each of tocainide's enantiomers but to look more closely at how the R-(-) and S-(+) changed over time and the response VPB's had to that change. The R-(-)

to S-(+) ratio did decrease in all patients over the study period, but the rate of change was different between subjects. This may have been due to stereo selective differences in tocainide metabolism and/or renal excretion. Sedman, et al, stated that protein binding between the two enantiomers is essentially the same and enantiomeric differences in absorption and volume of distribution are unlikely.<sup>4</sup> The differences in rate of change may have been due to disease states such as congestive heart failure and renal or hepatic dysfunction. At the beginning of the study, tocainide was given as a 1:1 stereoisomer. At one hour there was only a 5% difference in the two enantiomers but by the end of the study there was 50% more S-(+) enantiomer than R-(-) enantiomer. Sedman, et al, reported as much as four times more S-(+) enantiomer concentration over a period of three years.<sup>4</sup> With the short-term data collected in this study, we can support the theory that the R-(-) enantiomer is metabolized faster but we cannot extrapolate the extent of differences in R-(-) and S-(+) enantiomer concentrations that may occur beyond this study period.

In this study there was a correlation between mean tocainide concentration and mean percent of patients responding ( $r=0.84$ ,  $p < 0.01$ ). Since the R-(-) and S-(+) enantiomer concentrations changed with the total tocainide concentration, a correlation also existed between response and enantiomer concentrations. Correlation coefficient ( $r$ )

for the R-(-) enantiomer was 0.86  $p < 0.001$ ) and for the S-(+) enantiomer was 0.81 ( $p < 0.01$ ). From this information we could not conclude that efficacy was due to either of the two enantiomers but may have just as well been due to total tocainide concentration. However, if one looks at the mean R-(-):S-(+) ratio and mean percent reduction in VPBs, an inverse relationship does exist (Graph 8). Correlation coefficient ( $r$ ) for this data was -0.69 ( $p < 0.05$ ), suggesting that if we look at the R-(-):S-(+) ratio, we can see that as the ratio declines the percent of VPB suppression increases. The lowest ratio achieved in this study was 0.50 and whether the ratio continues to decline and the suppression of VPBs continues to increase cannot be extrapolated with the data available but may warrant further study.

Our data showed that there may be a delayed effect with tocainide. Looking more closely at the mean change in VPB's rather than percent of patients responding, interesting results have been observed. At one hour mean tocainide concentration was  $3.5 \pm 2.1$  mcg/ml and mean percent change in VPBs was only 21%. During the second hour concentration decreased to  $3.2 \pm 1.1$  mcg/ml but mean % reduction in VPB's increased to 35%. If the theory of delayed effect holds true, the increase in response at the second hour may be due to the serum concentration recorded of 3.5 mcg/ml during the first hour. Looking further at the fourth hour, another decrease in reduction of VPB's to only 22% does not



correlate with the simultaneous serum concentration increase to  $3.9 \pm 1.2$  mcg/ml, but may correlate with the drop in serum concentration that occurred at the second hour. Overall correlation coefficient (r) for simultaneous serum concentrations and percent reduction in VPB's is 0.71 ( $p < 0.05$ ) for total tocainide. Assuming that this delayed effect happens between one and four hours after a particular serum concentration is reached, and we look at the data collected every one to four hours, the correlation coefficient between tocainide concentration and percent reduction in VPB's becomes 0.90 ( $p < 0.05$ ). The data points may be too small to generally state that this phenomenon occurs in all patients but requires closer observation in future studies.

Explanation for the decrease in the serum concentration from  $7.8 \pm 2.7$  mcg/ml to  $6.0 \pm 1.5$  mcg/ml is beyond the scope of this paper. It may have been simply because there were only five patients left in the study during the last 8 hours.<sup>10</sup> Those patients who had dropped out of the study (5 non-responders and 5 no longer requiring treatment) had the higher serum concentrations which caused the mean concentration to be larger at other times in the study. All that is important is that the percent of responders and the percent reduction in VPB's decreased along with the concentration, which supports even more the theory that the serum concentration-antiarrhythmic effect relationship does exist.

## VI. CONCLUSIONS

The pharmacodynamic effects of tocainide and its enantiomers were evaluated to see if a correlation existed between mean serum concentrations and percent of patients responding or percent change in VPB's. Based on the analysis of the data collected in this study, our conclusions are as follows:

1. There is a statistically significant correlation between total tocainide concentration and percent of patients responding.
2. There is a statistically significant correlation between total tocainide concentration and percent suppression of VPB's.
3. There is a statistically significant correlation between the R-(-) or S-(+) concentration and percent suppression of VPB's or percent of patients responding could be determined.
4. There is a statistically significant inverse relationship between the R-(-):S-(+) ratio and the percent suppression of VPBs.

Although the above mentioned correlations were statistically significant, arrhythmia response to tocainide may have well been due to total concentration rather than either of the enantiomers alone.

TABLE I

## POPULATION CHARACTERISTICS

---

Number of Patients (n)	15
Age (yr)	60 $\pm$ 8
Males	13
Females	2
Weight (kg)	82 $\pm$ 22
CrCl (ml/min)	67 $\pm$ 38
Serum K <sup>+</sup> (mEq/L)	3.9 $\pm$ 0.5
Cardiac Disease	
Coronary	10
Cardiomyopathy	4
Valvular	1
CHF	6
Healed MI	6

---

## TABLE II

## LABORATORY SCREEN

Hematology

Hemoglobin  
Hematocrit  
WBC (total and differential)  
Platelets (estimate)

Blood Chemistry

SGPT  
SGOT  
LDH  
Alkaline Phosphatase  
Total Bilirubin  
Creatinine  
BUN  
Serum Cholesterol  
Serum Electrolytes (Na, K, Cl)

Urinalysis

Creatinine  
Specific Gravity  
pH  
Protein  
Sugar  
Microscopic: RBC's  
WBC's  
Casts  
Epithelials

TABLE III

TIME TABLE

	MINUTES										HOURS					
	ENTRY	2	15	30	1	2	4	8	12	16	24	32	40	48	Post	
Physical	X															X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X			X		X
12Lead EKG	X															X
Cardiac Monitoring																
Continuous throughout study period >																
Chest xray	X															X
Laboratory (Table II)	X															X
Plasma Conc	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

TABLE IV  
DATA ANALYSIS

1. SCATTER DIAGRAMS were drawn by plotting the following data:
  - a. Concentration of tocainide vs. percent reduction in VPBs
  - b. Concentration of tocainide vs. percent of patients responding
  - c. R:S ratio vs percent supression of VPB's
2. A CORRELATION COEFFICIENT (r) was derived to describe the degree of relationship between each of the following variables:
  - a. Concentration of tocainide and percent reduction in VPBs
  - b. Concentration of R-(-) enantiomer and percent reduction in VPBs
  - c. Concentration of S-(+) enantiomer and percent reduction in VPBs
  - d. Concentration of tocainide and percent of patients responding
  - e. Concentration of R() enantiomer and percent of patients responding
  - f. Concentration S(+) enantiomer and percent of patients responding
3. From the scatter diagrams, LINEAR REGRESSION was used to fit a straight line to the scatter of points

TABLE V

## MEAN DATA

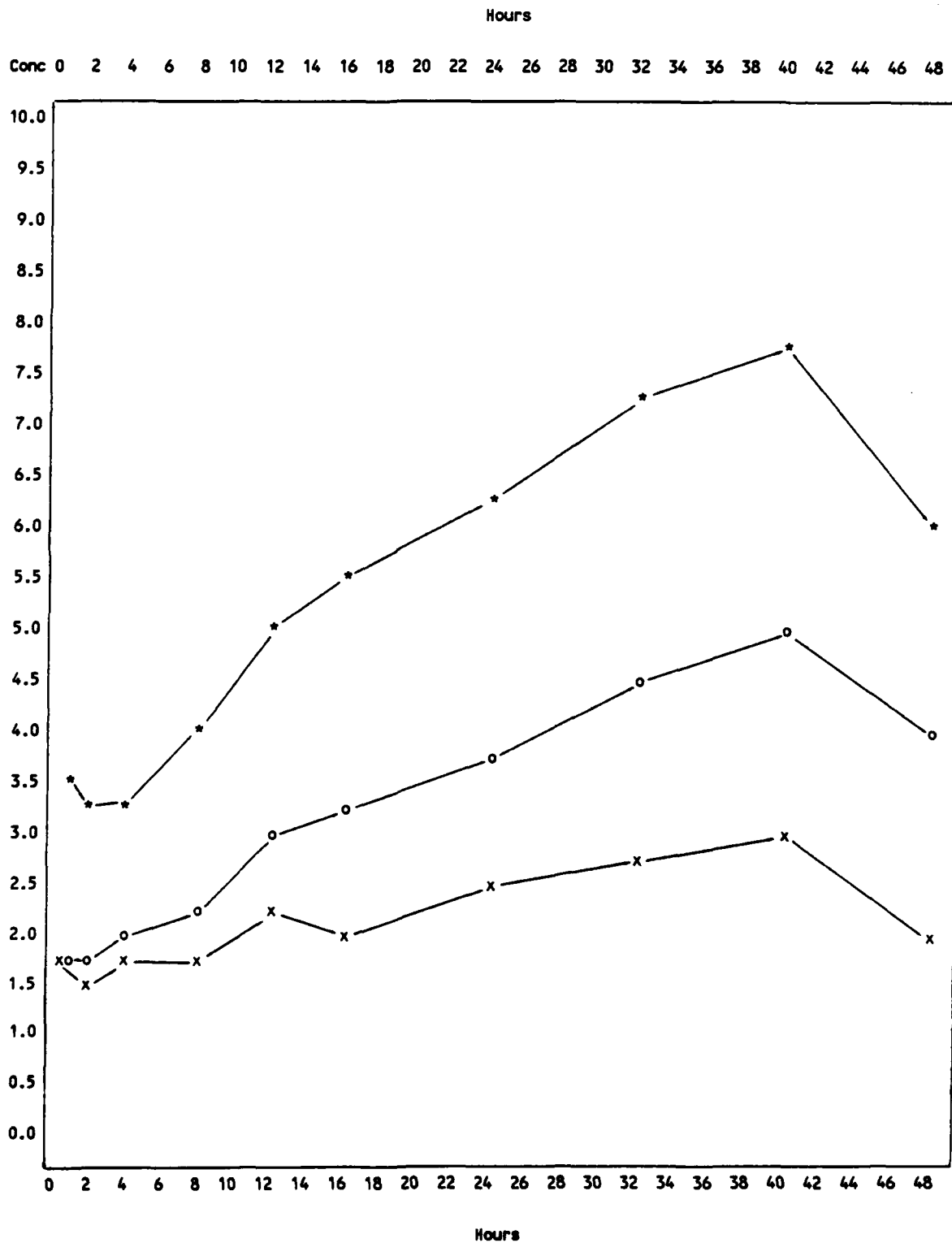
HOUR	TOCAINIDE CONC MCG/ML	R-(-) CONC MCG/ML	S(+) CONC MCG/ML	R/S RATIO	VPBs %	AVG % RESPONDERS
1	3.5±2.1	1.7±1.0	1.8±1.1	0.94	21	38
2	3.2±1.1	1.5±0.6	1.7±0.6	0.88	35	31
4	3.9±1.2	1.8±0.6	2.1±0.7	0.86	22	50
8	4.1±1.1	1.8±0.6	2.3±0.7	0.78	43	41
12	5.0±1.3	2.1±0.6	2.9±0.8	0.72	48	58
16	5.5±1.6	2.2±0.7	3.3±1.0	0.67	63	58
24	6.3±2.2	2.5±0.8	3.8±1.3	0.66	56	60
32	7.3±2.8	2.8±1.1	4.5±2.0	0.62	58	58
40	7.8±2.7	2.8±1.1	5.0±1.9	0.56	50	62
48	6.0±1.5	2.0±0.1	4.0±0.3	0.50	40	51

n = 15

GRAPH 1

MEAN TOTAL TOCAINIDE (x--x) MEAN 'R' (x--x) MEAN 'S' (o--o)

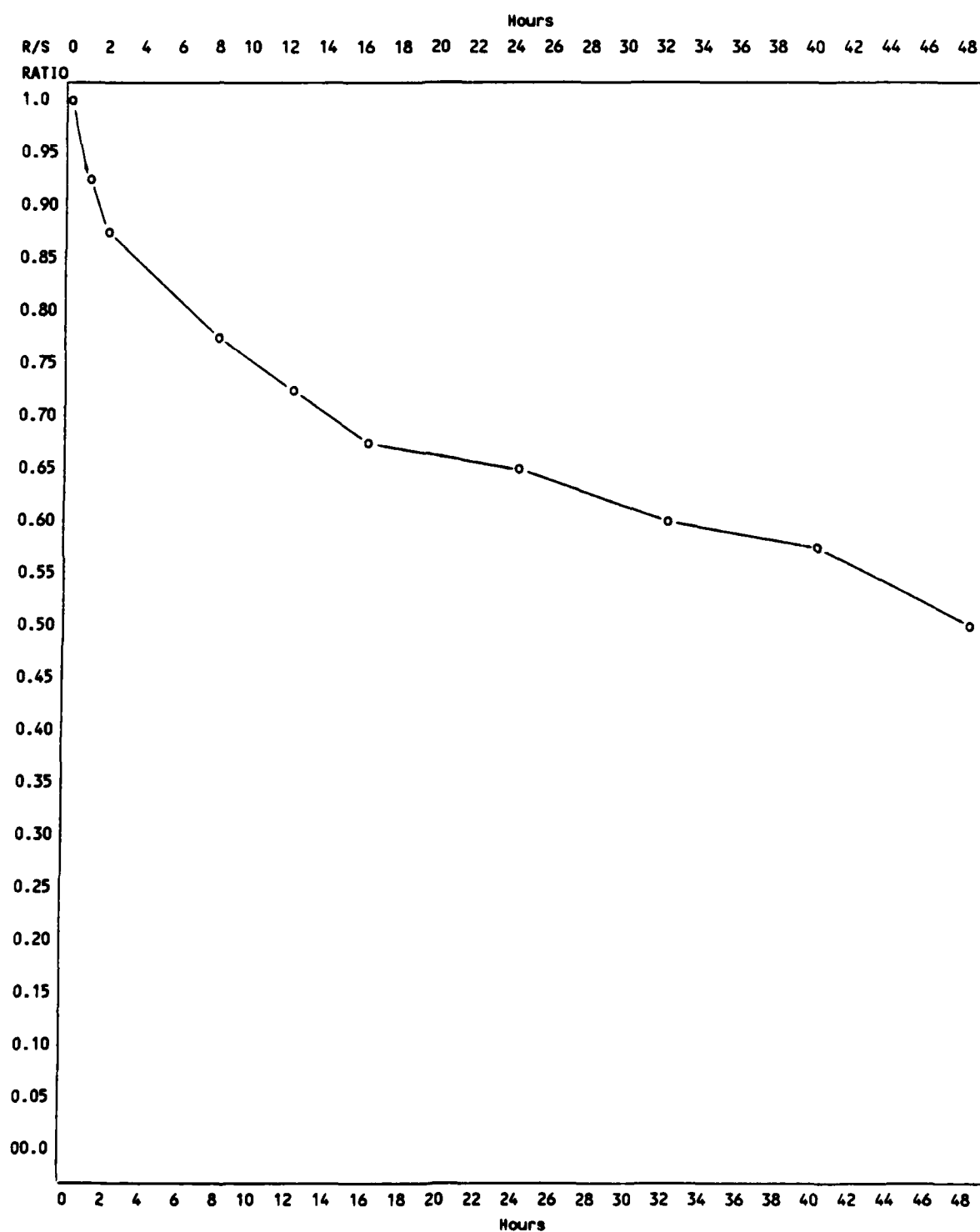
CONCENTRATION OVER STUDY PERIOD





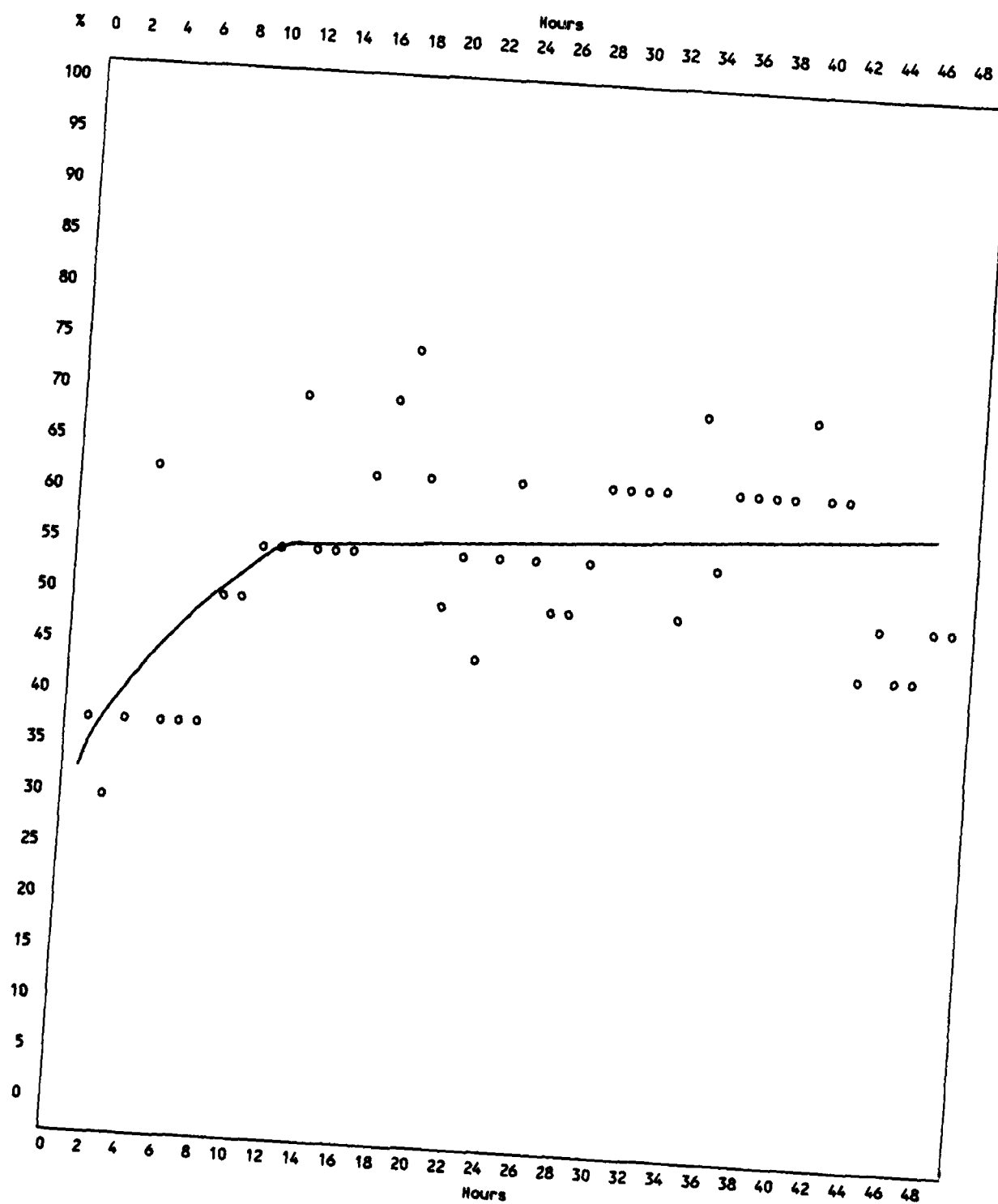
GRAPH 2

MEAN R/S RATIO OVER STUDY PERIOD



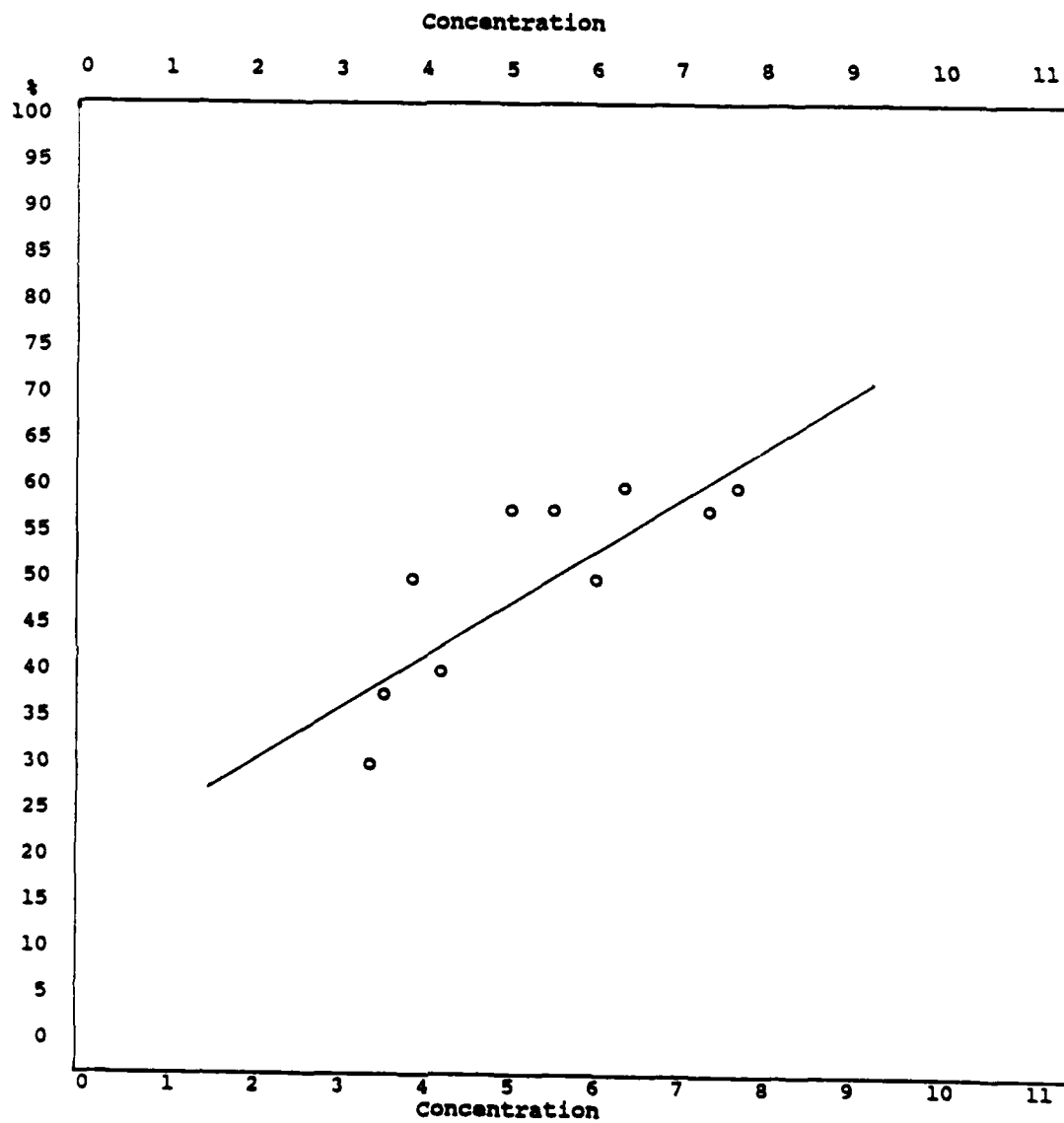
GRAPH 3

PERCENT OF PATIENTS RESPONDING OVER STUDY PERIOD



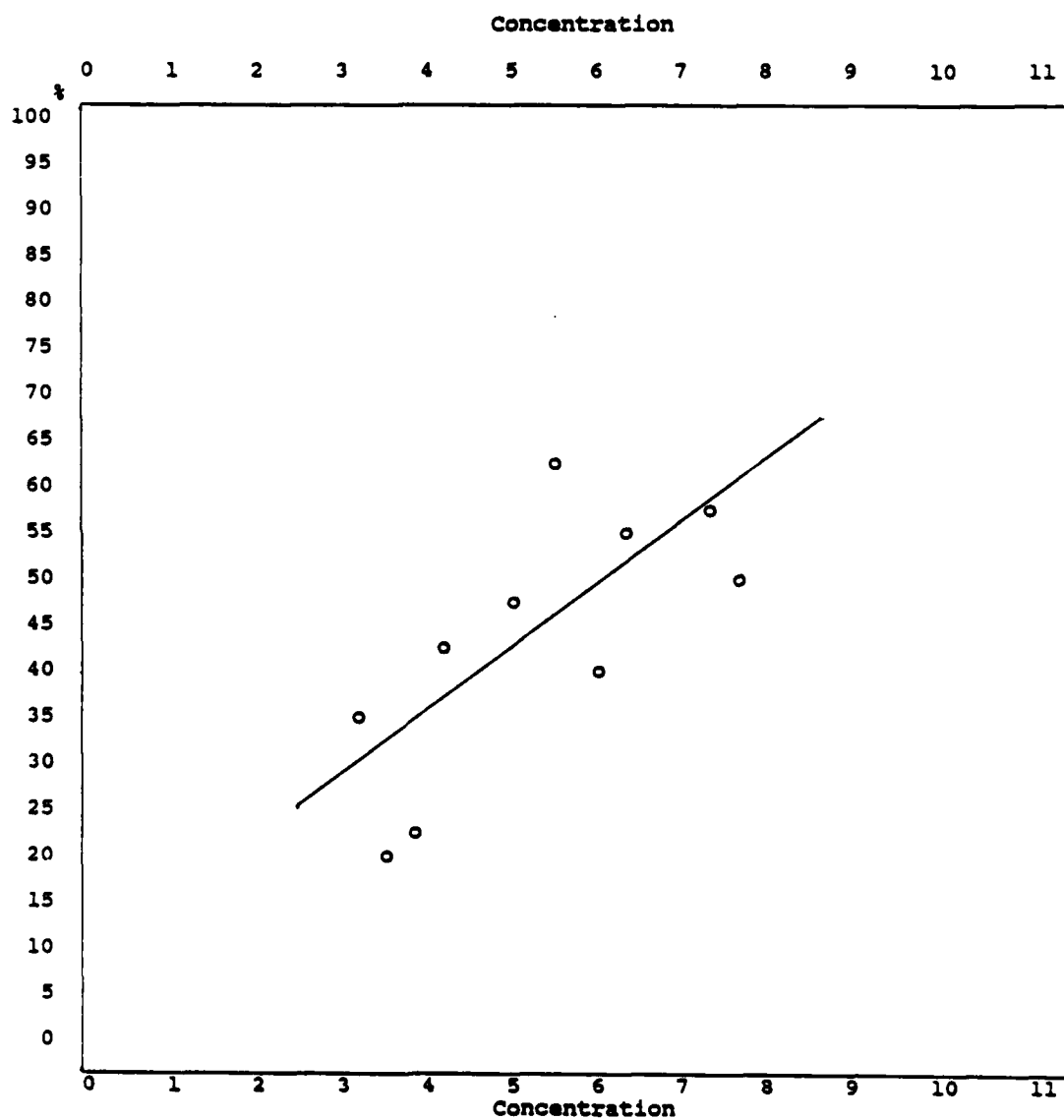
GRAPH 4

MEAN TOCAINIDE CONCENTRATION VS MEAN PERCENT PATIENT RESPONDING

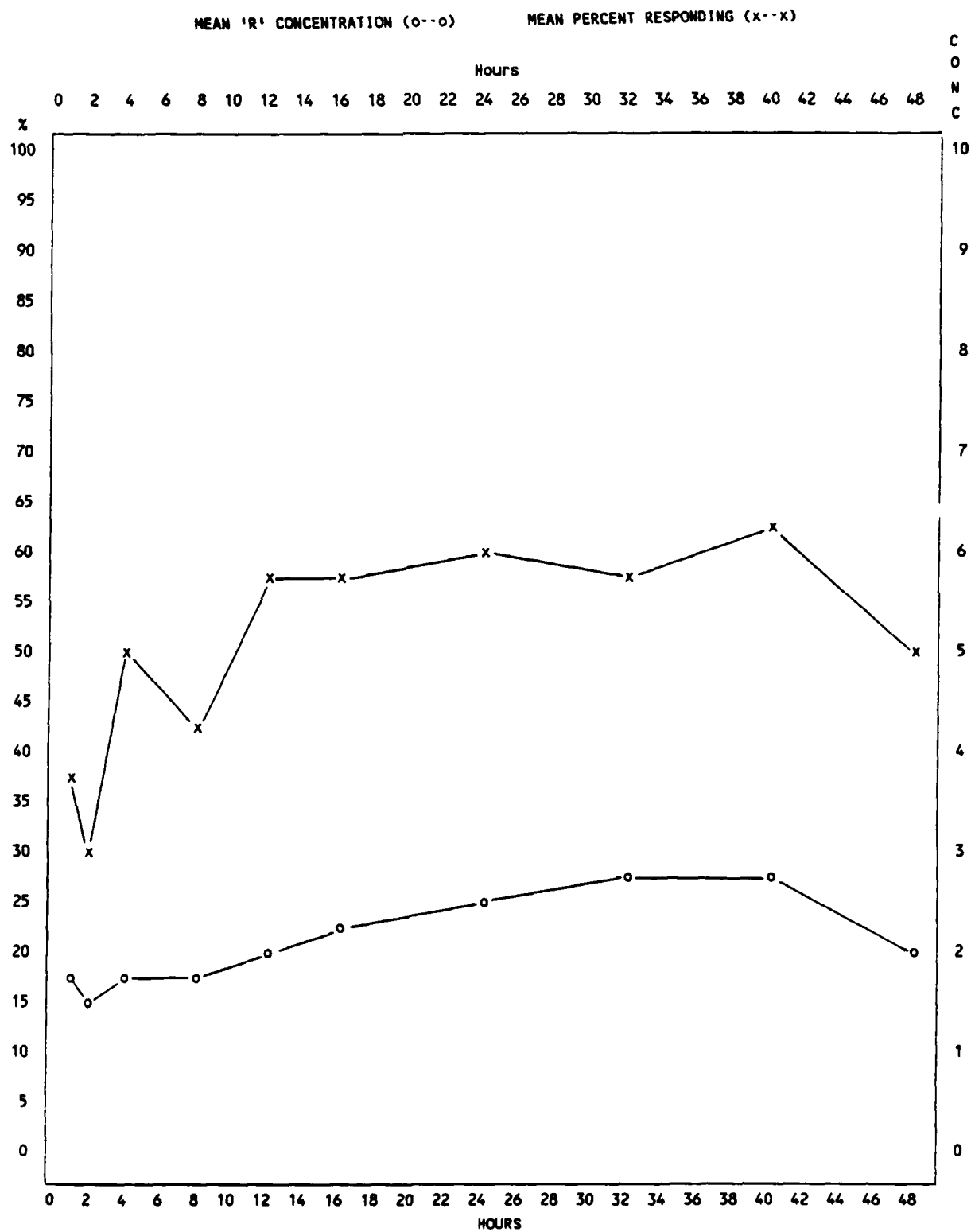


GRAPH 5

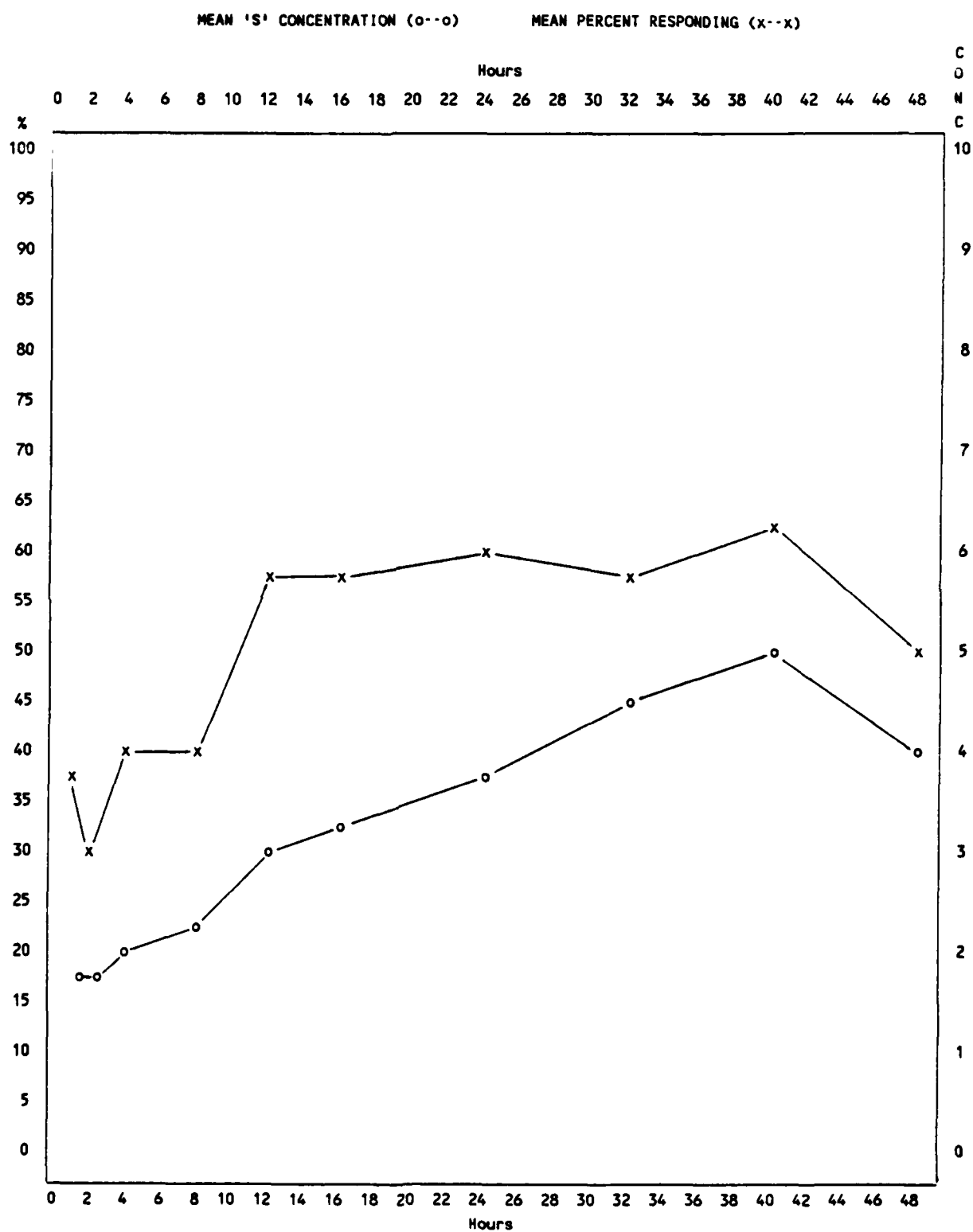
MEAN TOCAINIDE CONCENTRATION VS MEAN PERCENT SUPPRESSION OF VPBS



GRAPH 6

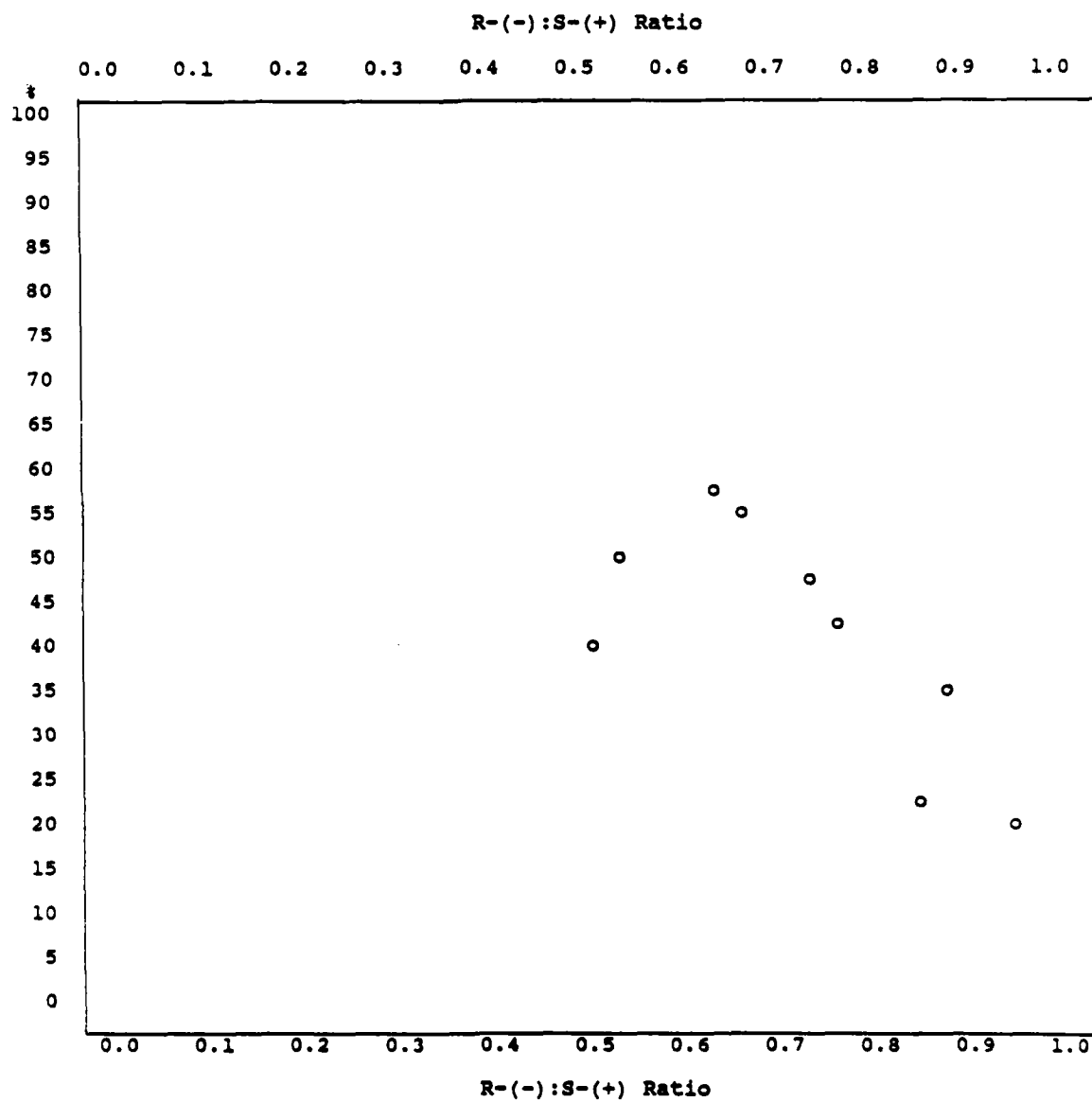


GRAPH 7



GRAPH 8

MEAN R-(-):S-(+) RATIO VS MEAN PERCENT SUPPRESSION OF VPBS



## REFERENCES

1. Morganroth J, Panidis IO, Harley S, Johnson J, Smith E, MacVaugh H. Efficacy and safety of intravenous tocainide compared with intravenous lidocaine for acute ventricular arrhythmias immediately after cardiac surgery. *Am J Cardiol* 1984;54:1253-1258.
2. Nyquist O, Forssell G, Nordlander R, Schenck-Gustafson K. Hemodynamic and antiarrhythmic effects of tocainide in patients with acute myocardial infarction. *Am Heart J* 1980;100(6):1000-1005.
3. Pottage A. Clinical profiles of newer Class I antiarrhythmic agents - tocainide, mexilitene, encainide, flecainide and lorcainide. *Am J Cardiol* 1983;52:24C-31C.
4. Sedman AJ, Gal J, Mastropaolo W, Johnson P, Maloney JD, Moyer TP. Serum tocainide enantiomer concentrations in human subjects. *Br J Clin Pharmac* 1984;17:113-115.
5. Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC. Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. *Circulation* 1976;54(6):844-889.
6. Byrnes WW, McMaster PD, Smith ER, Blair MR, Boyes RN, Duce BR, Feldman HS, Kronberg GH, Takman BH, Tenthorey PA. New antiarrhythmic agents. Primary alpha-amino anilides. *J Med Chem* 1979;22:1171-1176.
7. Roden DM, Reece SB, Higgins SB, Carr RK, Smith RF, Oates JA, Woosley RL. Tocainide therapy for refractory ventricular arrhythmias. *Am Heart J* 1980;100(1):15-21.
8. Harrison DC. Methods for documenting antiarrhythmic efficacy. *Am J Cardiol* 1983;52:37C-40C.
9. Follath F, Ganzinger U, Scheutz E. Reliability of antiarrhythmic drug plasma concentration monitoring. *Clin Pharmacol* 1983;8:63-82.
10. Venkataramanan R, Axelson JE. Dose-dependent pharmacokinetics of tocainide in the rat. *J Clin Exp Ther* 1980;215(1):231-234.
11. Morganroth J, Nestico PF, Horowitz LN. A review of the uses and limitations of tocainide - a Class IB antiarrhythmic agent. *Am Heart J* 1985;110(4):856-863.



12. Winkle RA, Mason JW, Harrison DC. Tocainide for drug-resistant ventricular arrhythmias: Efficacy, side effects and lidocaine responsiveness for predicting tocainide success. Am Heart J 1980;100(6):1031-1035.
13. Horn HR, Hadidian Z, Johnson JL, Vassallo HG, Williams JH, Young MD. Safety evaluation of tocainide in the American Emergency Use Program. Am Heart J 1980;100(6):1037-1040.

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